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NON-PHARMACOLOGICAL TREATMENT OF CHRONIC PAIN: A MULTIMODAL APPROACH

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Sommario

1. BACKGROUND

1.1 EPIDEMIOLOGY

Low back pain is one of the most common conditions worldwide. It has been reported as a major health and socioeconomic problem associated with work absenteeism, disability and high costs for patients, governments and health insurance companies [Airaksinen et al. 2006][1]; [Dagenais et al. 2008][2].

It is estimated that up to 84 percent of adults have low back pain at some time in their lives [Deyo & Tsui-WO 1987][3]; [Cassidy & Carrol 1998][4]. For many individuals, episodes of back pain are self-limited. Patients who continue to have back pain beyond the acute period (four weeks) have subacute back pain (lasting between 4 and 12 weeks) and may go on to develop chronic back pain (persists for ≥12 weeks) [Chou 2014][5]. In 2010, back symptoms were the principal reason for 1.3 percent of office visits in the United States [Centers for Disease Control and Prevention 2010][6]. Spinal disorders accounted for 3.1 percent of diagnoses in outpatient clinics. A 2012 systematic review estimated that the global point prevalence of activity-limiting low back pain lasting for more than one day was 12 percent and the one-month prevalence was 23 percent [Hoy et al. 2012][7]. Other survey estimates of the prevalence of low back pain have ranged from 22 to 48 percent, depending on the population and definition [Cassidy & Carrol 1998][4]; [Deyo et al. 2006][8]; [Skovron et al. 1994][9]; [Papageorgiou et al. 1995][10]. For example, the 2002 National Health Interview Survey found that 26 percent of respondents reported low back pain lasting at least one day in the last three months [Deyo et al. 2006][8].

1.2 LOW BACK PAIN

1.2.1 SPECIFIC LOW BACK PAIN

Although there are many etiologies of low back pain, the majority of patients seen in primary care will have nonspecific low back pain. The possible causes for a specific low back pain development are listed in the table below. This table is reproduced from Deyo [1986][11].

Mechanical Low Back Pain	Non-Mechanical Spine Disease	Visceral Disease
Lumbar strain **Degenerative disease** - Discs (spondylosis) - Facet joints (osteoarthritis) **Spondylolisthesis** **Herniated disc** **Spinal stenosis** **Fractures** **Congenital disease** - Severe kyphosis - Severe scoliosis **Spondylolysis** **Facet joint asymmetry**	**Neoplasia** - Multiple myeloma - Metastatic carcinoma - Lymphoma and leukemia - Spinal cord tumors - Retroperitoneal tumors **Infection** - Osteomyelitis - Septic discitis - Paraspinous abscess - Epidural abscess **Inflammatory arthritis** - Ankylosing spondylitis - Psoriatic spondylitis - Reactive arthritis - Inflammatory bowel disease **Osteochondrosis** **Paget disease**	**Pelvic organs** - Prostatitis - Endometriosis - Chronic pelvic inflammatory disease **Renal disease** - Nephrolithiasis - Pyelonephritis - Perinephric abscess **Aortic aneurysm** **Gastrointestinal disease** - Pancreatitis - Cholecystitis - Penetrating ulcer **Fat herniation of lumbar space**

Table 1.

1.2.2 NON-SPECIFIC LOW BACK PAIN

The vast majority of patients seen in primary care (>85 percent) have nonspecific low back pain, meaning that the patient has back pain in the absence of a specific underlying condition that can be reliably identified [Deyo & Weinstein 2001][12]; [Chou et al. 2007][13]; [Chou et al. 2011][14]. Many of these patients may have musculoskeletal pain [Chou 2014][5]. Most patients with nonspecific back pain improve within a few weeks.

Despite its high prevalence, the source of pain is not established in the majority of cases and the term 'non-specific LBP' is widely used [Hancock et al. 2007][15]; [Niemisto et al. 2004][16]; [Niemisto et al. 2005][17]; [Panjabi et al. 2003][18]. Non-specific LBP has been reported as the most common type of low back pain and is defined as low back pain not attributed to a recognizable or specific pathology, such as nerve root compromise or serious spinal pathology (i.e. fracture, cancer and inflammatory diseases) [Airaksinen et al. 2006][12]; [Van Tulder et al. 2006][19].

1.2.3 RISK FACTORS

Risk factors associated with back pain complaints include smoking, obesity, age, female gender, physically strenuous work, sedentary work, psychologically strenuous work, low educational

attainment, Compensation insurance, job dissatisfaction, and psychologic factors such as somatization disorder, anxiety, and depression [Cassidy & Carrol 1998][4]; [Skovron et al. 1994][20]; [Katz 2006][21]; [Deyo et al. 1990][22]; [Croft et al. 1995][23]; [Croft et al. 1999][24]; [Macfarlane et al 1997][25]; [Steffens et al. 2015][26].

1.3 ETIOLOGIES

1.3.1 SYSTEMIC ETIOLOGIES

Among patients who present with back pain to primary care settings, less than 1 percent will have a serious systemic etiology [Deyo et al. 2006][8]; [Jarvik & Deyo 2002][27].

1.3.1.1 SPINAL CORD OR CAUDA EQUINA COMPRESSION

There are many causes of cauda equina syndrome, the most common being herniation of the intervertebral disc. One systematic review found that cauda equina syndrome was caused by herniation of the intervertebral disc in 22.7 percent of cases [Sun JC et al. 2014][28], while the incidence of cord compression in patients known to have cancer varies depending on the cancer, among patients who are diagnosed with cord compression, it is the initial manifestation of malignancy in 20 percent [Schiff et al. 1997][29].

Pain is usually the first symptom of cord compression, but motor (usually weakness) and sensory findings are present in the majority of patients at diagnosis. Bowel and/or bladder dysfunction are generally late findings.

1.3.1.2 METASTATIC CANCER

The bone is one of the most common sites of metastasis. A history of cancer is the strongest risk factor for back pain from bone metastasis [Deyo & Diehl 1988][30].

Pain is the most common symptom. In patients with a history of cancer, sudden, severe pain raises concern for pathologic fracture. Patients may also have neurologic symptoms from either spinal cord compression or spinal instability.

1.3.1.3 SPINAL EPIDURAL ABSCESS

It is a rare, but serious, cause of back pain. Initial symptoms (eg, fever and malaise) are often nonspecific. Over time, localized back pain may be followed by radicular pain and neurologic deficits. Risk factors include recent spinal injection or epidural catheter placement and injection drug use.

Immunocompromised patients may also be at higher risk. Urgent antibiotic treatment and surgical therapy for those with neurologic symptoms is required.

1.3.1.4 VERTEBRAL OSTEOMYELITIS

The incidence of vertebral osteomyelitis generally increases with age. Men are more commonly affected than women. Many cases are thought to be health care-related or postprocedural from hematogenous spread of bacteremia. Less specific risk factors include an immunocompromised state and injection drug use.

Acute osteomyelitis typically presents with gradual onset of symptoms over several days. Most patients with vertebral osteomyelitis will present with back pain but may not have fevers or other systemic symptoms. Prompt antibiotic treatment improves outcomes.

1.3.2 SPECIFIC ETIOLOGIES

Less than 10 percent of patients who present in primary care settings with low back pain will have less serious but specific etiologies for their pain [Jarvik & Deyo 2002][27]; [Underwood 1995][31].

1.3.2.1 VERTEBRAL COMPRESSION FRACTURE

Approximately 4 percent of patients presenting in the primary care setting with low back pain will have a vertebral compression fracture [Jarvik & Deyo 2002][27]. There may be no history of preceding trauma. Risk factors for osteoporotic fracture include advanced age and chronic glucocorticoid use.

1.3.2.2 RADICULOPATY

Radiculopathy refers to symptoms or impairments related to a spinal nerve root. Damage to a spinal nerve root may result from degenerative changes in the vertebrae, disc protrusion, and other causes. The clinical presentations of lumbosacral radiculopathy vary according the level of nerve root or roots involved.

Patients present with pain, sensory loss, weakness, and/or reflex changes consistent with the nerve root involved.

1.3.2.3 SPINAL STENOSIS

Lumbar spinal stenosis is most often multifactorial. Spondylosis spondylolistheses, and thickening of the ligamentum flavum are the most common causes, typically affecting patients >60 years.

Ambulation-induced pain localized to the calf and distal lower extremity resolving with sitting or leaning forward is a hallmark of lumbar spinal stenosis. Other symptoms of lumbar spinal stenosis can include back pain and sensory loss and weakness in the legs, though many patients may present with a normal neurologic exam. Symptoms of neurogenic claudication can usually be distinguished from vascular claudication.

1.3.3 OTHER ETIOLOGIES

1.3.3.1 ANKYLOSING SPONDYLITIS

Among patients who present in primary care settings for back pain, it is estimated that approximately 0.5 percent will have ankylosing spondylitis [Jarvik & Deyo 2002][27]; [Underwood 1995][31]. It is most commonly diagnosed in men under the age of 40 years. Almost all patients report back pain, which often has characteristics suggesting an inflammatory etiology (morning stiffness, improvement with exercise, pain at night) [Chou 2014][5]. Patients may also have extraskeletal disease manifestations (eg, uveitis).

1.3.3.2 OSTEOARTHRITIS

Low back pain may be a symptom of osteoarthritis of the facet joints spine. Patients may also complain of hip pain, either from osteoarthritis of the hip or referred pain from the spine. Osteoarthritis most commonly presents in patients over the age of 40. Pain is typically exacerbated by activity and relieved by rest. Osteoarthritis can lead to spinal stenosis.

1.3.3.3 SCOLIOSIS AND HYPERKYPHOSIS

Back pain can be associated with serious scoliosis and hyperkyphosis.

1.3.3.4 PSYCHOLOGIC DISTRESS

Psychologic distress (eg, depression or somatization) may contribute to the severity symptoms of low back pain or may be a cause of nonorganic back pain [Chou 2014][5].

1.3.3.5 PIRIFORMIS SYNDROME

The piriformis syndrome is thought by some to be a condition in which the piriformis muscle, a narrow muscle located in the buttocks, compresses or irritates the sciatic nerve [Ropper & Zafonte 2015][32]; [Papadopoulos & Khan 2004][33]; [Hopayian el al. 2010][34].

1.3.3.6 SACROILIAC JOINT DYSFUNCTION

Sacroiliac joint dysfunction, a term to describe pain in the region of the sacroiliac joint believed to be due to malalignment or abnormal joint movement, is a controversial topic. Diagnosing this condition is difficult due to the absence of an agreed upon gold standard [Szadek et al. 2009][35]. Tests of pelvic symmetry or sacroiliac joint movement have been shown to have low intertester reliability [Potter & Rothstein 1985][36]; [Russel et al. 1981][37]; [Freburger & Riddle][38]; [Levangie 1999][39]; [McCombe et al. 1989][40]; [Slipman et al. 1998][41]; [Riddle & Freburger 2002][42] and provocative manoeuvres such as guided injections of the sacroiliac joint have been unreliable in diagnosis and treatment [Slipman et al. 1998][41]; [Irwin et al. 2007][43]; [Juch et al. 2017][44].

1.4 ACUTE LOW BACK PAIN

In acute pain, the strengthening of the pain pathway is represented by specific neurophysiological mechanisms of short-term peripheral and central sensitization [Nijs J et al. 2010][45].

Peripheral sensitization is linked to the activation of latent nociceptors and a lowering of the nociceptor threshold that result in a tissue inflammatory response. When tissue damage is created, a series of chemical mediators converge, and elements of the immune system have effects also on the nervous system. In this condition the peripheral receptors lower their activation threshold, therefore they become more receptive leading to a peripheral sensitization that results in two possible variants [Nijs et al. 2010][46]:

- Primary hyperalgesia: a condition where a normally painful stimulus is perceived to be more painful;
- Primary allodynia: a condition where painless stimuli are perceived to be painful.

In central sensitization the dorsal horn lamina neurons amplify their signal, lower their activation threshold for the painful stimuli brought from the periphery towards the centre by the C fibres, and increase their own fields of painful signal reception locally.

The problem of increased pain perception does not occur only at the lesion's level, but also in neighbouring areas because the central representation of pain is less specific for the confluence of afferent fibres [Manchikanti et al. 2010][47].

Once the allogenic damage has healed, the strengthening of painful transmission ceases because our organism has again reached homeostasis and there is therefore an adaptive response [Nijs et al. 2010][46].

1.5 CHRONIC LOW BACK PAIN

Chronic pain affects physiological, psychological and social well-being of people [Gureje et al. 1998][48]; [Varassi et al. 2008][49] and the World Health Organization (WHO) recognizes it as a public health problem throughout the world. It is usually defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage that has been lasting for at least 12 weeks [Merskey et al. 2011][50]. Chronic pain dramatically contributes to disability, anxiety, depression, sleep disturbances, poor quality of life, and healthcare costs [Leadley et al. 2014][51]; [Moore et al. 2014][52]; [Park et al. 2012][53].

Since pain refers to a multimodal experience, the chronicity of pain can have dramatic impacts on various aspects of people's life. It has been reported indeed that chronic pain is associated with a deterioration of several domain of people's quality of life, such as role limitations due to physical or mental health, vitality, social functioning and general health [Leadley et al. 2014][54].

Moreover, it has been demonstrated that chronic pain can lead to a somatic disperception, meaning a substantial mismatch between the sensation of the affected body part and its actual physical state [Flor et al 1997][55]; [Moseley 2008][56]; [Forderreuther et al. 2004][57]; [Lewis et al. 2007][58]. [Flor at al. 1997][19] showed an enhanced reactivity and a somatotopic reorganization of the somatosensory cortex in patients with chronic low back pain, hypothesizing an important role in the persistence of the painful experience. Indeed, Maihofner et al. [2004][59] demonstrated that this cortical reorganization reversed with clinical improvement of painful sensations. Disruption of painful body parts perception have later been demonstrated in patients suffering from chronic low-back pain and complex regional pain syndrome [Forderreuther et al. 2004][21]; [Lewis et al. 2007][22]; [Moseley 2008][20]. In these studies, patients reported a distorted body image, or in some cases a disruption of their body sensation.

Since the clinical rating of pain relies on the subjective reports of patients, a distorted body image could lead to an incorrect pain rating, which could in turn lead to an incorrect pain treatment and to the risk of drug abuse. There is thus the need for the development of alternative non-pharmacological treatments of chronic pain to improve patients' quality of life, reduce pain and reduce drug intake.

1.6 VIRTUAL REALITY

Virtual reality (VR) constitutes a technological rehabilitation tool that allows the user to experience and interact with a computer-generated environment, which provides several advantages over standard care: it allows the simulation of realistic environments and real-life exercises; these environments and activities can be personalized to meet the specific needs of the patient; patients feel more motivated by this kind of virtual environment [Rizzo and Kim 2005][60], which is an important factor that can influence rehabilitation and performance outcome [Thornton et al. 2005][61]. VR constitutes an enriched environment with augmented multiple sensory feedback and information (auditory, visual, tactile). Thanks to this enriched environment, VR rehabilitation engages several cortical and subcortical neuronal circuits that potentiate patient's learning and recovery. First, in some simple motor rehabilitation exercises, the motor copy strategies use mirror neurons system to improve learning. Mirror neurons are neurons that fire both when a subject acts and when the subject observes the same action being performed by another [Rizzolatti et al. 1996][62]. They have been localized in the ventral premotor cortex, although other mirror neurons have been individuated in the supplementary motor area, the primary somatosensory cortex and the inferior parietal cortex. Mirror neurons are particularly involved in the mechanisms of perception/action coupling and are fundamental in the processes of understanding actions of other people and for learning new skills by imitation [Rizzolatti et al. 2008][63]. Moreover, thanks to the online and final feedbacks given to the subject during VR training, this latter has a developed knowledge of results and the knowledge of his/her performance, which constitute the basis for reinforcement learning, where basal ganglia play a central role. Lastly, the presence of virtual teachers and guidance engages another type of learning: the supervised learning, where the cerebellum plays a central role.

VR would thus constitute a good candidate to help patients to augment their perceived movements and body positions [Harvie et al. 2017][64] in order to regain a correct body image. VR enriched environment has already proven some efficiency in reducing chronic pain either during the VR exercises [Jones et al. 2016][65] or after 3 to 10 days of rehabilitation [Thomas et al. 2016][66]; [Ylevar et al. 2017][67], providing thus evidence for safety and possible efficacy of such treatments. However, so far, no studies have investigated the effects of such treatment in longer periods or have reported the effects of VR therapy on the patient's quality of life or on other cognitive and functional aspects.

According to the above mentioned framework, we hypothesize that VR training could help patients to restore a correct body image and improve patient's quality of life, reduce pain sensations, and improve patients' mood and sensorimotor abilities.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of the study is to assess the effect of VR treatment on the quality of life of subjects with chronic low back pain. The primary endpoint that relates to this objective is change from evaluation PRE (week -02) to evaluation POST (week 06) of the SF36 - Short Form Health Survey.

2.2 SECONDARY OBJECTIVES

The secondary objectives are to evaluate the personality traits and cognitive functions of people with chronic low back pain. We also aim at assessing the effects of VR rehabilitation on pain intensity, mood, sensorimotor abilities, and drug intake.

3. METHODS

3.1 STUDY DESIGN

3.1.1 STUDY OVERVIEW

VR-CHRPAIN is a single arm prospective study in chronic pain subjects.

Subjects received virtual reality-based sensorimotor rehabilitation treatment twice a week, for six consecutive weeks. Subjects were evaluated at baseline (PRE) and after six weeks of rehabilitation (POST).

The total duration of study participation for each subject was approximately 10 weeks, including pre evaluation, treatment and post evaluation.

3.2 STUDY SPECIFICS

3.2.1 OVERALL STUDY DURATION

The study consisted of six specific phases:

- Evaluation PRE (at week -02)
- Level of Activity assessment PRE (from week -02 to week 00)
- Treatment (from week 00 to week 05)
- Evaluation POST (at week 06)
- Level of Activity assessment POST (from week 06 to week 08)

3.3 EVALUATIONS

Evaluations were performed at three time points:

- PRE (at week -02)
- POST (at week 06)

Each evaluation consisted of a neurological or physiatrist examination, a detailed neuropsychological examination and a physical examination.

3.4 ASSESSMENT OF LEVEL OF ACTIVITY

The level of activity assessment consisted of two specific phases:

- Level of Activity PRE (weeks -02 and -01) ➔ (2 weeks)
- Level of Activity POST (weeks 06 and 07) ➔ (2 weeks)

During the level of activity assessment phase, subject weared h24/24 for two consecutive weeks a smartband (Garmin Forerunner 235) which tracked their day and night activity, i.e. total number of steps, calories burnt and quality of sleep.

The watch was removed only to recharge the battery (approximately 3 hours) every 4/5 days.

3.5 TREATMENT

The treatment lasted for 6 consecutive weeks (week 0 to week 5) and consisted of two sessions a week (total n=12), each session lasting 1 hour.

3.6 SELECTION OF SUBJECTS

To be eligible to participate in this study, candidates must meet the following eligibility criteria at screening:

3.7 INCLUSION CRITERIA – CHRONIC LOW BACK PAIN

- Aged 18-75;
- History of chronic pain ≥ 12 weeks.

3.8 EXCLUSION CRITERIA – LOW BACK PAIN

- Informed consent negation;
- Systemic metabolic/neurological/muscular degenerative disorder;
- Systemic infection;
- Cardiopulmonary/pulmonary disorder with contraindication to exercise;
- Recent spinal surgery (<12 months);
- Spinal stenosis/spondylolisthesis/spinal pathology/spinal fracture;
- Acute radiculopathy/nerve root compromise;
- Neuropathic pain;
- Pregnancy.

3.9 ENROLLMENT AND REGISTRATION

Subjects provided written informed consent before any evaluation tests are performed. During the PRE evaluation (week -02), subjects completed the neurological or physiatrist, neuropsychological and physical examinations to determine study eligibility.

Patients were enrolled at the Unit of Rehabilitation and Functional Recovery (Head: Dr. S. Iannaccone), the San Raffaele Hospital via Olgettina 60, Milan.

3.10 TREATMENTS

Treatments consisted of virtual reality-based sensorimotor rehabilitation provided using the Virtual Reality Rehabilitation System (VRRS) of the Khymeia group.

The equipment includes a computer workstation connected to a 6 degrees of freedom (DOF) motion-tracking system (Polhemus G4, Vermont, US), a high-resolution LCD displaying the virtual scenarios on a large screen and a software processing the motion data coming from the receiver of the end-effector placed on the sternum or pelvis movements.

The VRRS allows the participant to perform the requested motor tasks, while the movement of the system's end-effector is simultaneously represented in a virtual scenario.

3.11 CHRONIC LOW BACK PAIN REHABILITATION

Exercises were done by isolating the movement of the trunk among to pelvis. Two sensors were positioned on subject's body (sternum and pelvis).

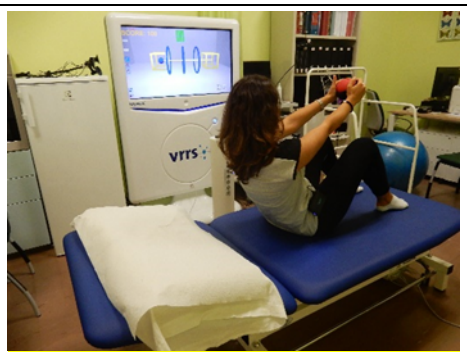
Subjects saw on a virtual reality screen an avatar moving in accordance with the body sensors movements. The aim of the exercises was to regain a correct body control by isolating the movement, moving only one sensor and leaving the other still in a specific position.

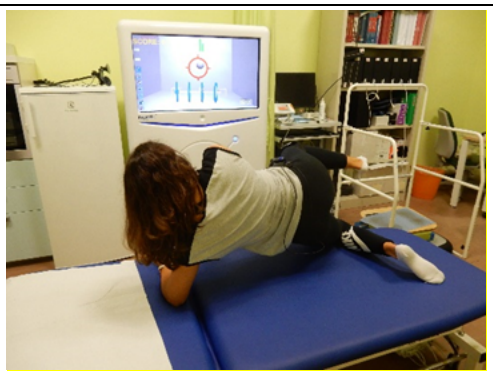
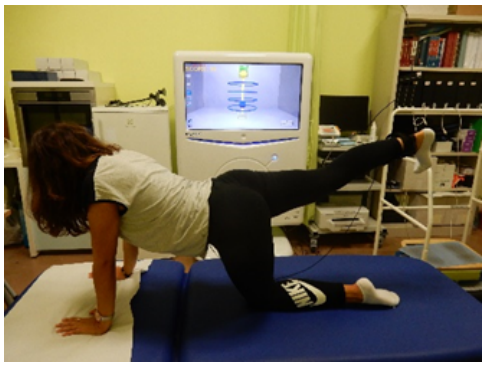
<table>
<tr><th></th><th>EXERCISES</th><th colspan="2">PICTURES</th></tr>
<tr><td rowspan="3">TRUNK ROTATION</td><td rowspan="2">The exercise consisted in a rotation (unilateral or bilateral) in standing position with foot on the floor in natural position (i) tandem (ii), pad surface (iii), monopodial balance (iv).</td><td>  </td><td>  </td></tr>
<tr><td>  </td><td>  </td></tr>
<tr><td rowspan="2">The exercise consisted in a rotation (unilateral or bilateral) in sitting position on a chair (i), pad surface or Bobath ball (ii).</td><td colspan="2">  </td></tr>
<tr><td colspan="2">  </td></tr>
</table>

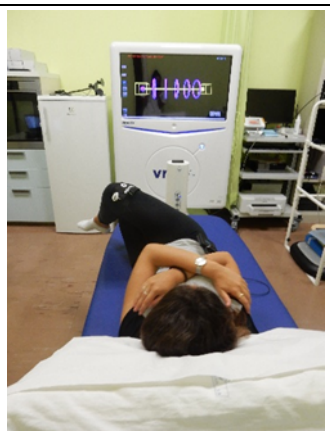
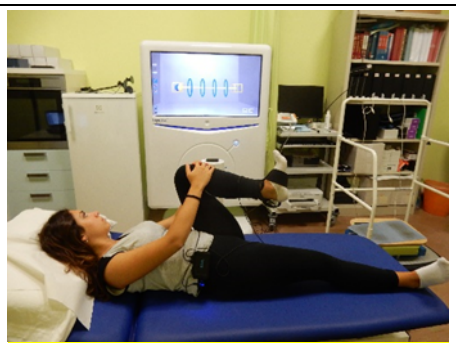
	The exercise consisted in a rotation (unilateral or bilateral) kneeling on a physiotherapy bed (i).	
	The exercise consisted in a lateral flexion (unilateral or bilateral) in half-kneeling position on a physiotherapy bed (i).	
LATERAL FLEXION	The exercise consisted in a lateral flexion (unilateral or bilateral) in standing position with foot on the floor in natural position (i), tandem (ii), pad surface (iii), monopodial balance (iv).	   
	The exercise consisted in a lateral flexion (unilateral or bilateral) in sitting position on a chair (i), pad surface or Bobath ball (ii).	

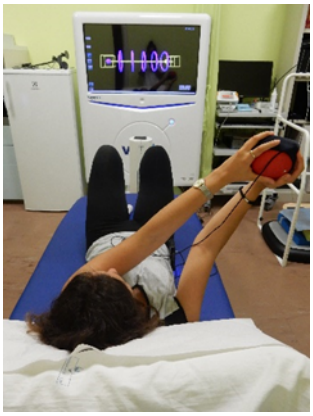
		
	The exercise consisted in a lateral flexion (unilateral or bilateral) kneeling on a physiotherapy bed (i).	
	The exercise consisted in a lateral flexion (unilateral or bilateral) in half-kneeling position on a physiotherapy bed (i).	
ANTERIOR FLEXION	The exercise consisted in an anterior flexion (unilateral or bilateral) in standing position with foot on the floor in natural position (i), tandem (ii), pad surface (iii), monopodial balance (iv).	   

	The exercise consisted in an anterior flexion (unilateral or bilateral) in sitting position on a chair (i), pad surface or Bobath ball (ii).	 
EXTENSION	The exercise consisted in an extension (unilateral or bilateral) in standing position with foot on the floor in natural position (i), tandem (ii), pad surface (iii), monopodial balance (iv).	   
	The exercise consisted in an extension (unilateral or bilateral) in sitting position on a chair (i), pad surface or Bobath ball (ii).	 

<table>
<tr><td rowspan="2">BALANCE</td><td rowspan="2">The exercise consisted in balance exercises with audio-visual feedback</td><td>  </td><td>  </td></tr>
<tr><td colspan="2">  </td></tr>
<tr><td rowspan="2"></td><td>CRUNCH: Patient in supine position, with legs bent, raise the head and shoulder off the ground</td><td colspan="2">  </td></tr>
<tr><td>REVERSE CRUNCH: Patient in supine position, with legs straight. Then patients were asked to bend them knee and flex the hips towards the trunk.</td><td colspan="2">  </td></tr>
</table>

STRENGHT AND CORE STABILITY	OBLIQUE PLANK: Patient is side-lying with knee bent/straight. Patient rised his pelvis horizontally with support on elbows and knee/legs. In order to add some destabilizing forces, patients were asked to flex gleno-humeral joint (a) or the contralateral hip and knee (b).	 
	BIRD-DOG: Patient in quadruped position with elbow locked straight and head in neutral position. Patient pulled in the belly button and lifts one leg off the floor so that the limb is in line with the trunk and then the opposite side arm is lifted off the ground.	
	BRIDGE: Patient in supine position with knee bent, head and shoulder on the ground. Patient rised him pelvis, with support of feet and back. Then patient tried to rise one leg keeping the position	
	FRONTAL PLANK: Patient is prone with knee straight and feet pointed at the ground. patient rised his pelvis with support of elbows and feet.	

	SQUAT: Patient is in standing position and were asked to bend and extend them lower limb.	
MOBILITY	Patient in supine position with lower limbs bended on the bed. Patients were asked to rotate them trunk in right and left directions with (i) and without (ii) weight.	
		
	Patient lying in supine position and were asked to bend alternatively one leg to the sternum.	

	Patient lying in supine position and were asked to bend both legs to the sternum.	
	Patient in a supine position with knees and hips flexed at 90 °, hammer feet and hands in the popliteal fossa. Patients were asked to extend them knees (i), or extend them knees while them head were flexed simultaneously (ii).	 
	Patient lying in supine position with upper arms raised. Subjects were asked to keep a weight and perform trunk rotations.	

3.12 STUDY PROCEDURES

3.12.1 EVALUATIONS

Neurological or physiatrist exam:

- Anamnesis (only in PRE);
- Eligibility for the study criteria (only in PRE);

- Pharmacological history / consumption:
    - Diary: a diary was given to the subject during the PRE evaluation so that the participant had to report their drug intake during the whole study duration.

Neuropsychological assessments:

- Neuropsychological anamnesis (only in PRE);
- Cognitive functions: Activities of Daily Living (ADL) / Instrumental Activities of Daily Living (IADL); Mini Mental State Examination (MMSE); Token test; Semantic fluency; Phonemic fluency; Digit span test; Digit Span Backward; Corsi block-tapping test; Rey Complex Figure Test; Raven's Progressive Matrices; Attentional Matrices; Trail making test; Stroop test; Wisconsin Card Sorting test;
- Personality test: Minnesota multiphasic personality inventory test (MMPI);
- Depression: Beck Depression Inventory-II;
- Quality of life: SF36 - Short Form Health Survey.

Physical therapy assessments:

- Physical anamnesis;
- Evolution of the onset;
- Breeding and Worsening factors;
- Clinical examination / tests;
- Activity limitation / Participation restriction: Roland and Morris Disability Questionnaire;
- Function: Lumbar Active Range of Motion;
- Pain: Numeric Rating Scale; McGill Pain Questionnaire; Brief Pain Inventory (Short Form);
- Level of Activity assessment: Smartband (Steps, calories count, sleep).

3.13 OUTCOMES

3.13.1 PRIMARY OUTCOME

Quality of life (QoL) was the primary outcome of this study. QoL was assessed by the SF36 - Short Form Health Survey (SF-36). The SF-36 is a generic patient-reported outcome measure aimed at quantifying health status, and is a standard questionnaire widely used in the literature to measure health-related quality of life. The SF-36 comprises eight health scales: physical functioning (10 items), role limitations–physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role limitations–emotional (3 items), and mental health (5 items).

Two core dimensions of health, physical and mental, can be derived from these eight scales [Anderson et al. 1996][68]. Each of the 8 summed scores is linearly transformed onto a scale from 0 (negative health) to 100 (positive health) to provide a score for each subscale. Each subscale can be used independently. The MCID has not been determined.

3.13.2 SECONDARY OUTCOMES

- **Roland and Morris Questionnaire:** The Roland-Morris Disability Questionnaire (RDQ) is a health status measure designed to be completed by patients to assess physical disability due to low back pain. It was designed for use in research, e.g. as an outcome measure for clinical trials, but has also been found useful for monitoring patients in clinical practice. It was originally designed for use in primary care in the UK, but has been used in a variety of settings [Roland and Morris 1983][69]. The RDQ score is calculated by adding up the number of items checked. The scores therefore ranges from 0 (no disability) to 24 (maximum disability)[70] [Jordan et al. 2006][71]. Validation and Italian version used is found in this article [Padua et al. 2002][72].

The Minimal Clinically Important Difference was determined as the change of 30% or 3 point change.

- **Kinematic Data:** Kinematic data were measured by isolating the movement from pelvis to trunk. Data obtained from movement were relative to them maximal rotation, flexion, extension and lateral flexion.

Lumbar Active Range of Motion (AROM) were measured by Polhemus G4 magnetic field.

- **Numeric Rating Scale:** The Numeric Rating Scale is a segmented numeric horizontal bar on which patients select a whole number (from 0 “no pain” to 10 “worst possible pain”) that best reflects the intensity of their pain at rest and on movement. It has become a widely used instrument for pain screening and is ubiquitous as a screener in many health care environments [Hartrick et al. 2003][73]; [Farrar et al. 2001][74].

The Minimal Clinically Important Difference has been established by [Pool et al. 2007][63] as a change of 2.5 points from baseline.

- **McGill Pain Questionnaire:** The McGill Pain Questionnaire is a self-report measure of pain studied with a number of diagnoses. The McGill Pain Questionnaire assesses both the quality and intensity of subjective pain. The McGill Pain Questionnaire is composed of 78 words, of which respondents choose those that best describe their experience of pain. A maximum of seven words

are selected from the following categories: dimension 1 to 10 (pain descriptors), three words; dimensions 11 to 15 (affective components of pain) two words, dimension 16 (evaluation of pain) one word, and dimension 17 to 20 (miscellaneous) one word. Scores are tabulated by summing values associated with each word; scores range from 0 (no pain) to 78 (severe pain). Qualitative differences in pain may be reflected in respondent's word choice [Melzack 1975][75].

The MCIDs for the three indices of the MPQ (pain rating index, total number of words selected, and PPI) have not been determined.

- **Patient's Global Impression of Change:** The Patient Global Impression of Change scale is recommended for use in chronic pain clinical trials as a core outcome measure of global improvement with treatment. The scale measures the change in patient's overall status since the beginning of the study on a scale of: 1 (very much improved); 2 (much improved); 3 (minimally improved); 4 (no change); 5 (minimally worse); 6 (much worse); and 7 (very much worse) [Dworkin et al. 2005][76]. This measure is a single-item rating by participants of their improvement with treatment during a clinical trial on a 7-point scale that ranges from 'very much improved' to 'very much worse' with 'no change' as the mid-point. The data provide a responsive and readily interpretable measure of participants' assessments of the clinical importance of their improvement or worsening over the course of a clinical trial.

- **Pharmacological Diary:** Each subject received a personal pharmacological daily that was filled with the name of drug taken and the dosage. The aim is to monitor and assess if there is a reduction of the drug dosage assumption.

Drugs prescribed by neurologist were not be changed during the study phases, the drugs taken 'as needed' (PRN pro re nata) were monitored by each subject filling a specific daily diary during all the study phase (15 weeks – 105 days).

- **Beck Depression Inventory-II:** The BDI-II is a 21-item self-report instrument assessing the common cognitive symptoms of depression, and is considered a valid and reliable instrument for depression screening in the general population [Beck et al. 1996][77]. The BDI-I1 is scored by summing the highest ratings for each of the 21 items. Each item is rated on a 4-point scale ranging from 0 to 3, and the total scores can range from 0 to 63. BDI-I1 total scores ranging from 0 to 13 represent "Minimal" depression; total scores from 14 to 19 are "Mild;" total scores from 20 to 28 are "Moderate;" and total scores from 29 to 63 are "Severe."

The NICE guidelines suggest the smaller criterion for clinically important differences of 2 BDI-II points for treatment-resistant depression compared to a criterion of 3 points in new episodes of depression [NICE 2004][78].

- **Level of Activity:** Level of activity on chronic pain patients were evaluated tracking the daily subject's number of steps, calories count and sleep cycle by the waterproof smartband iHealth Wave AM4.

- **Minnesota Multiphasic Personality Inventory:** The MMPI-2 is a 567-item, true-false questionnaire that evaluates personality on 3 validity and 10 clinical scales. For each scale, a T-score of 65 is considered the level of clinical significance in the 95th percentile [Bigal et al. 2003][79]. The MMPI is the most widely used personality inventory and is commonly employed in the assessment of musculoskeletal chronic pain patients [Turk et al. 1995][80].

3.14 PATIENT SAFETY

From the first articles published in the literature on virtual reality rehabilitation, only few cases of mild, minor Adverse Events have been reported.

The most commonly reported Adverse Events regarding the intensive use of virtual reality are:

- Nausea;
- Vomiting;
- Headache;
- Eyestrain.

Of these Adverse Events, mild non-disabling and regressive spontaneously in the short term have been reported by [Rosa et al. 2016][81]. Also [Bart et al. 2010][82] investigated the effects of virtual reality on a population of children aged 6 to 12 years, without reporting severe Adverse Events.

3.15 DEFINITION OF ADVERSE EVENT AND SERIOUS ADVERSE EVENT

An Adverse Event (AE) is any untoward occurrence in a patient or clinical investigation subject administered a virtual reality rehabilitation session and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the virtual reality.

A Severe Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death.
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires patient's recovery or prolongation of existing recovery.
- Results in persistent or significant disability/incapacity.

3.16 SEVERITY OF EVENT

Mild: Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.

Moderate: Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.

Severe: Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

3.17 RELATIONSHIP OF EVENT TO STUDY TREATMENT

Not related: An AE were considered "not related" to the use of the virtual reality rehabilitation system if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to: the lack of reasonable temporal relationship between virtual reality treatment and the event, the presence of a biologically implausible relationship between the treatment and the AE, or the presence of a more likely alternative explanation for the AE.

Related: An AE were considered "related" to the use of the virtual reality rehabilitation system if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to: a positive rechallenge, a reasonable temporal sequence between the virtual reality treatment and the event and a biologically plausible relationship between the virtual reality treatment and the AE, or a lack of an alternative explanation for the AE.

3.18 MONITORING AND RECORDING EVENTS

Any Adverse Event experienced by the subject between the time of first session of study treatment and the Evaluation-POST visit is to be recorded on the Case Report Form, regardless of the severity of the event or its relationship to study treatment.

3.19 TEMPORARY OR DEFINITIVE TREATMENT DISCONTINUATION

All the patients were assessed, independently of their compliance with the treatment, with the aim to be able to perform an INTENTION TO TREAT (ITT) analysis. If a patient interrupted the treatment protocol, he/she were asked to perform the post-treatment assessment even so. In this case data were considered for the PER-PROTOCOL analysis.

The Shapiro – Wilk test was used to check the normality of the clinical variables, according to these results parametric or non-parametric test were used for studying differences within the group. Height of statistical threshold level were set at $p < 0.05$.

4. ETHICAL AND REGULATORY CONSIDERATIONS

4.1 ETHICAL REQUIREMENTS

The Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines.

4.2 DECLARATION OF HELSINKI

The study was carried out in conformity to the Declaration of Helsinki and in agreement with the Italian law regulations (Legislative Decree n. 211/2003; Ministry Decree 17 December 2004) on experimental procedures in health care.

4.3 ETHICS COMMITTEE

The Investigator must obtain Ethics Committee approval of the protocol and other required study documents prior to starting the study.

It is the responsibility of the Investigator(s) to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

5. DATA MANAGEMENT

5.1 CASE REPORT FORM (CRF)

It is the responsibility of the Investigators to collect and maintain all the documentation of the study in an adequate storage system. A Case Report Form (CRF) folder was used for each patient. CRFs should be used to record study data and are an integral part of the study. The CRF must therefore be legible and compiled using a black ink ball pen.

For each recruited patient, including those who interrupt the study for any reason, CRF must be completed and signed by the Investigator. The reasons why a patient interrupted the study should be reported by the Investigator in the CRF section on the study interruption.

The CRF should contain all the patient-related information at each stage of the study. Patients were not identified by name, but with an appropriate continual numeric code and only use the initials of the patient.

Errors should be crossed but not deleted.

5.2 MONITORING OF THE STUDY

The Clinical Monitor visited the Investigator(s) at regular intervals during the study and after the study has completed, as appropriate.

During these visits, CRFs and supporting documentation related to the study were reviewed and any discrepancies or omissions were resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

6. DATA PROTECTION

The subject were not identified by name in the CRF or in any study reports and these reports were used for research purposes only.

7. PARTICIPANTS

20 patients (11 female, mean age 47.5 ± 15.3 y.o., age range [19-72]) presenting with chronic low back pain were included (mean pain duration 35.0 ± 42.4 months, range [3-144], see Table 1 for patients' description). Inclusion criteria were: (1) age between 18 and 75 years, and (2) history of chronic pain ≥ 12 weeks. Exclusion criteria were: (1) systemic metabolic disorder, (2) neurological or muscular degenerative disorder, (3) systemic infection, (4) cardiopulmonary or pulmonary disorder with contraindication to physical exercise, (5) recent spinal surgery (<12 months), (6) s spinal pathologies such as stenosis or spondylolisthesis or fracture, (7) acute radiculopathy or compromised nerve root, (8) pregnancy.

The study was approved by the local Ethics Committee and all participants signed an informed consent according to the Declaration of Helsinki before entering the survey.

Table 1: Description of the sample. LBP: low-back pain. F: female, 132 M: male. Age is expressed in years, and pain duration is expressed in months.

Patients	Age	Gender	Pain duration
LBP-1	57	F	48
LBP-2	53	M	24
LBP-3	71	M	19

LBP-4	50	F	8
LBP-5	58	M	120
LBP-6	42	F	3
LBP-7	19	M	16
LBP-8	64	M	144
LBP-9	45	F	48
LBP-10	45	F	4
LBP-11	48	M	120
LBP-12	42	M	5
LBP-13	26	F	5
LBP-14	55	F	4
LBP-15	69	F	17
LBP-16	28	F	24
LBP-17	72	F	24
LBP-18	44	F	12
LBP-19	30	M	24
LBP-20	32	M	30

8. EVALUATION

All the patients had a neurological or physiatrist visit and none of them had any indication for surgery.

Patients had negative electromyographic evaluations for acute pathology. Before and after treatment, subjects underwent a comprehensive neuropsychological assessment and a physical therapy examination.

During the neuropsychological assessment, the following tests for different cognitive domains and questionnaires for daily living activities were administered: (1) Activities of Daily Living (ADL) [Katz et al. 1963][83], (2) Instrumental Activities of Daily Living (IADL) [Lawton et al. 1969][84], (3) Mini Mental State Examination (MMSE) [Folstein et al. 1975][85], (4) Attentive and Raven Matrices [Raven 2003][86], (5) Token test [De Renzi & Vignolo 1962][87], (6) Semantic fluency 144 [Novelli et al. 1986][88], (7) Phonemic fluency [Novelli et al. 1986][88], (8) naming [Miceli et al. 1994][89], (9) word picture matching test [Keplan et al. 1983][90], (10) Digit span test [Orsini et al. 1987][91], (11) Digit Span

Backward [Wechsler et al. 1945][92], (12) Corsi block-tapping test [Corsi 1972][93], (13) Rey Complex Figure Test [Carlesimo et al. 1996][94], (14) Trail making test [Reitan 1955][95], (15) Stroop test [Jensen & Rohwer][96], (16) Wisconsin Card Sorting test [Heaton et al. 1993][97], (17) personality (Minnesota multiphasic personality inventory test 2 (MMPI-2, only in pre)) [Sellbom et al. 2008][98], (18) depression (Beck Depression Inventory-II) [Beck et al. 1996][99], (19) quality of life (SF36 - Short Form Health Survey) [Ware & Sherbourne 1992][100]. This is a measure of health status contemplating eight sections: "vitality", "physical functioning", "bodily pain", "general health perceptions", "physical role functioning", "emotional role functioning", "social role functioning", "mental health"[[Ware & Sherbourne 1992][100]; [McHorney 1994][101].

During the physical therapy exam, the functional and pain assessment included: (1) an 11-point numeric rating scale (NRS) [Hartcick et al. 2003][102], (2) the McGill Pain Questionnaire (MPQ) [Melzack 1975][103], (3) the Brief Pain Inventoy (short form) (BPI) [Cleeland & Ryan 1994][104], and (5) the Roland and Morris Disability Questionnaire (RMDQ) [Roland & Morris 1983][105]. Kinematic data were also measured using the Polhemus G4 tracking system and consisted in measuring the maximal and the average trunk's range of motion during ten consecutive rotations, flexions, extensions and lateral flexions [Roosink et al. 2015][106]; [Willigenburg et al. 2013][107].

After treatment, patients were also asked to report their Global Impression of Change (GIC) on a 7-point categorical scale [Farrar et al. 2001][108].

9. TREATMENTS

Patients underwent 12 rehabilitative sessions of 1 hour each over a period of 4 to 6 weeks.

Treatments consisted in virtual reality-based sensorimotor rehabilitation provided by the Virtual Reality Rehabilitation System (VRRS) of the Khymeia group (Noventa Padovana, Italy). The technological equipment includes a computer workstation connected to 166 a 6 degrees of freedom (DOF) motion tracking system (Polhemus G4, Vermont, US), a high-resolution LCD displaying the virtual scenarios on a large screen and a software processing the motion data. These data are issued by the receiver of the end-effector placed on the sternum or the hips.

The VRRS allowed the participant to perform the requested motor tasks, while the movement of the system's end-effector is simultaneously represented in a virtual scenario. In this scenario, an avatar

reproduces online the performance of the patient who also gets an immediate visual and acoustic feedback on his/her performance. Indeed, for each exercise, the patient has to reach a certain result.

The performance of the patient is immediately codified in terms of score, color code and acoustic feedback so that the patient always has a knowledge of performance and result. The aim of the exercises was to regain a correct body image by improving the control of single movements of the trunk. Patients underwent a series of exercises consisting mainly in trunk rotation, flexion and extension realized in various positions (standing, sitting, and kneeling) as displayed in Figure 1.

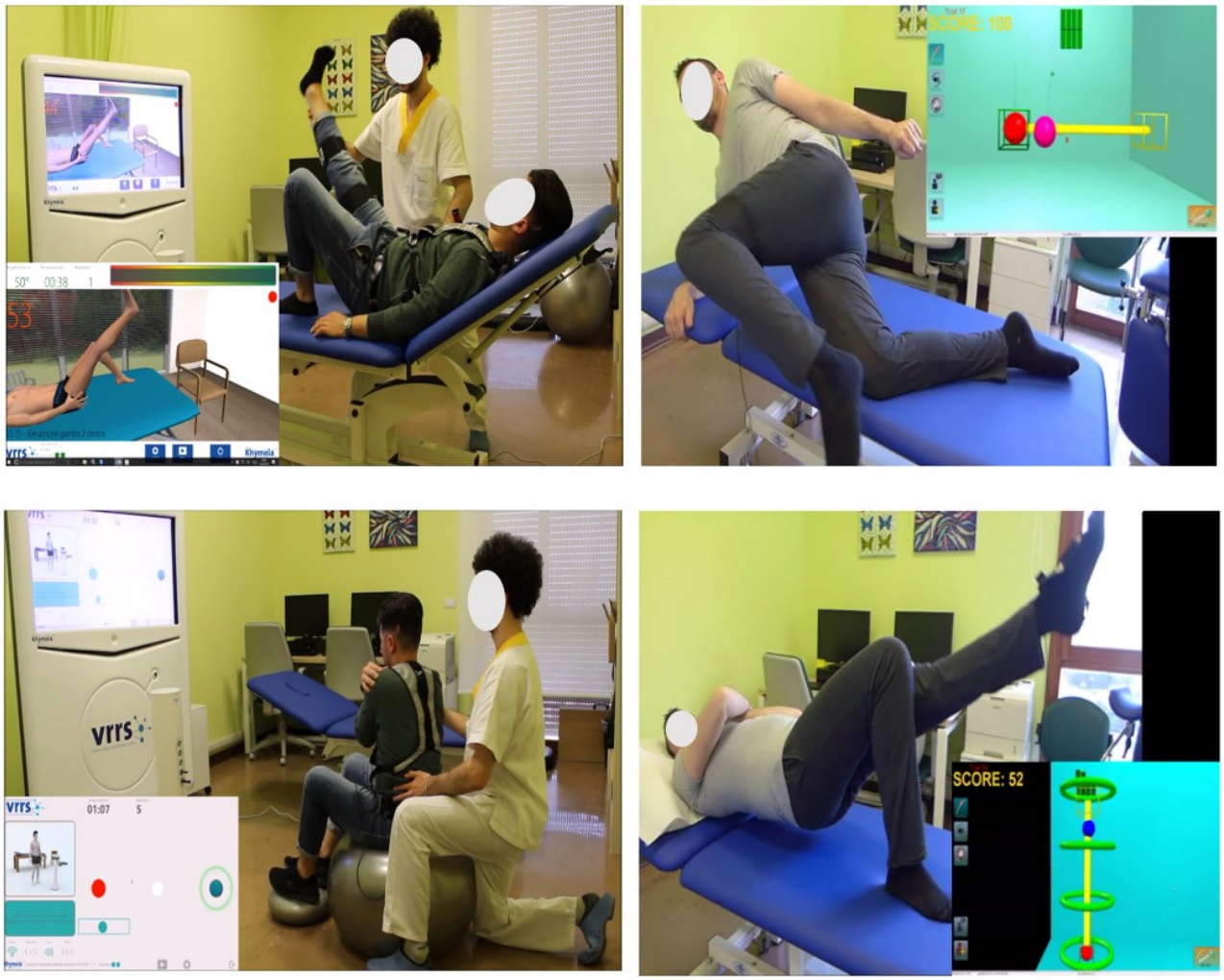


Figure 1: Rehabilitation set-up: figure displays participants undergoing rehabilitation sessions using the virtual reality system, under the supervision of a physiotherapist. Subjects wore sensors on hips or sternum and were asked to perform movements in front of the computer where an avatar and virtual objects reproduced online the virtual movements. The system provided patients with immediate multisensory knowledge of results and performance.

10. STATISTICAL CONSIDERATIONS

10.1 SAMPLE SIZE CALCULATION

Power size calculation was done on primary outcome SF36 - Short Form Health Survey. The SF36 - Short Form Health Survey is a numerical scale that comprises eight health scales: physical functioning, role limitations–physical, bodily pain, general health, vitality, social functioning, role limitations–emotional, and mental health. Two core dimensions of health, physical and mental, can be derived from these eight scales. Each of the 8 summed scores is linearly transformed onto a scale from 0 (negative health) to 100 (positive health) to provide a score for each subscale. Each subscale can be used independently.

Considering the SF36 - Short Form Health Survey Physical Health Dimension mean difference within pre and post as a change of 7.7 points and standard deviation of 10.7 [Macedo et al. 2012][109], 5% type I error (α=0.05), 80% power (β=0.2) and 15% of dropout rate has been established a targeted sample size of 20 participants. Sample size calculation has been done by PS Power and Sample Size Calculation software.

10.2 DEMOGRAPHY AND BASELINE CHARACTERISTICS

Demographics and baseline data were summarized with statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

10.3 DESCRIPTIVE ANALYSES

Data were analyzed to describe the variability of motor and neuropsychological aspects of chronic pain patients. The patient's Global Impression of Change were analyzed as descriptive.

10.4 INTRAGROUP COMPARISON, ADVERSE EVENTS ANALYSES

All the motor and neuropsychological outcomes, referred to the primary and secondary objectives, were analyzed by intragroup comparison.

Repeated Measures ANOVA, or Conover test in case the data will not be distributed in Gaussian form, were used to analyse all data with principal factor TIME (2 levels: Evaluation PRE and Evaluation POST).

10.5 CORRELATIONS

Investigate the correlation between the variations of the motor and cognitive scales in order to verify whether there is an influence between motor and cognitive functions and vice versa.

To investigate the correlation between motor and cognitive variables, the Spearman or Pearson correlation coefficient were used depending on the data normality.

11. RESULTS

11.1 GLOBAL IMPROVEMENT AND PAIN RATINGS

Every patient completed the sessions of virtual reality rehabilitation without side effects. Eighteen out of the twenty patients reported an improvement on the NRS pain scale (Table 2). Indeed, Wilcoxon test showed a significant improvement in NRS pain rating after treatment ($p<0.001$). This improvement in NRS pain score correlated with the improvement reported by the patients on the GIC scale (Spearman $R= -0.638$, $p=0.002$). Indeed, 16 patients reported improvement on the GIC scale (from slight to extreme improvements) and 3 patients reported an impression of no change.

Significant improvements at the McGill Pain Questionnaire were also observed for the total pain score (Pain Rating Index-Total, PRI-TOT, $p=0.001$) and the number of words used to described the pain (Number of Words Chosen, NWC, $p=0.001$). The Brief Pain Inventory also reported significant improvements at the mean interference score ($p<0.001$), and at the worst and average pain scores (respectively, $p= 0.002$ and $p<0.001$), while no difference was observed for the least pain score ($p=0.077$).

Table 2: Pain evaluations. Data are expressed in mean ± standard deviations or medians and (in parenthesis) first and third quartiles, depending on data normality. NRS: 11-point numeric rating scale; McGill Pain Questionnaire: PRI-TOT: Pain Rating Index-Total; NWC: Number of Words Chosen.

*: significant differences between pre and post values.

Tests		Pre	Post	P value
NRS pain		7.5 (5.0 to 8.38)	3.0 (1.63 to 6.5)	<0.001 *
McGill Pain Questionnaire	PRI-TOT	31.85 ± 12.17	23.35 ± 16.70	0.001 *
	NWC	12.6 ± 4.56	9.05 ± 6.07	0.001 *
Brief Pain Inventory	Interference score	59.36 ± 20.45	34.70 ± 29.94	<0.001 *
	Worst pain	66.02 ± 19.12	46.58 ± 31.0	0.002 *
	Average pain	55 (35 to 70)	35 (15 to 50)	<0.001 *
	Least pain	30 (10 to 55)	5 (0 to 40)	0.077

11.2 QOL, MOOD, NEUROPSYCHOLOGICAL EVALUATION AND PSYCHOLOGICAL PROFILE

Results are displayed in Table 3. The statistical analyses of the SF-36 revealed significant improvements in 5 out of the 8 the subscale scores. Indeed, significant improvements were observed in: (1) “physical functioning” (p=0.018), “physical role functioning” (p=0.04), (3) “bodily pain” (p=0.029), (4) “vitality” (p=0.015), and (5) “social role functioning” (p=0.028). There was also a trend for an improvement in “emotional role functioning” (p=0.062). There were significant correlations between the improvements in quality of life and improvements in pain scores. In particular, improvements in “physical functioning” correlated significantly with improvements in: (1) NRS scores (R= -0.521, p=0.047), (2) McGill pain score PRI-TOT (R= -0.550, p=0.034), and (3) BPI average pain (R= -0.673, p=0.008) and worst pain (R= -0.563, p=0.036). Improvements in “physical role functioning” correlated with improvements in: (1) McGill number of words chosen (NWC, R= -0.545, p=0.036), and (2) BPI worst pain (R= -0.544, p=0.044). Improvements in “vitality” correlated with BPI average pain improvements (R= -0.627, p=0.016). Improvements in “social role functioning” correlated with: GIC scores (R=0.599, p=0.018), (2) improvements in NRS scores (R= -0.545, p=0.036), (3) McGill PRI-TOT (R=-0.575, p=0.025), and (4) BPI interference score (R= -0.650, p=0.012).

Lastly, a significant post-treatment improvement of the Beck Depression Inventory-II scores was found (p=0.04).

Table 3: Evaluation of mood and quality of life. Data are expressed in mean ± standard deviations or medians and (in parenthesis) first and third quartiles, depending on data normality. BDI: Beck Depression Inventory. SF-36: Short Form Health Survey. Results are exposed according to the 8 subscales: PF: Physical Functioning; PR: Physical Role Functioning; BP: Bodily Pain; GH: General Health; VT: Vitality; SR: Social Role functioning; ER: Emotional Role functioning; MH: Mental Health.

* shows significant differences between pre and post values.

Tests		**Pre**	**Post**	**P value**
BDI		13.5 (9.0 to 19.0)	3.5 (2.25 to 17.75)	0.037 *
SF-36	PF	49.67 ± 20.83	63.67 ± 20.04	0.018 *
	PR	0.0 (0.0 to 25.0)	0.0 (0.0 to 75.0)	0.040 *
	BP	28.53 ± 18.16	42.27 ± 22.38	0.029 *
	GH	50.67 ± 21.44	50.50 ± 25.76	0.996
	VT	40.67 ± 15.45	51.0 ± 18.92	0.015 *
	SR	44.97 ± 24.43	57.33 ± 31.27	0.044 *
	ER	0.0 (0.0 to 33.33)	33.33 (0.0 to 100)	0.062
	MH	57.87 ± 14.57	63.73 ± 22.80	0.183

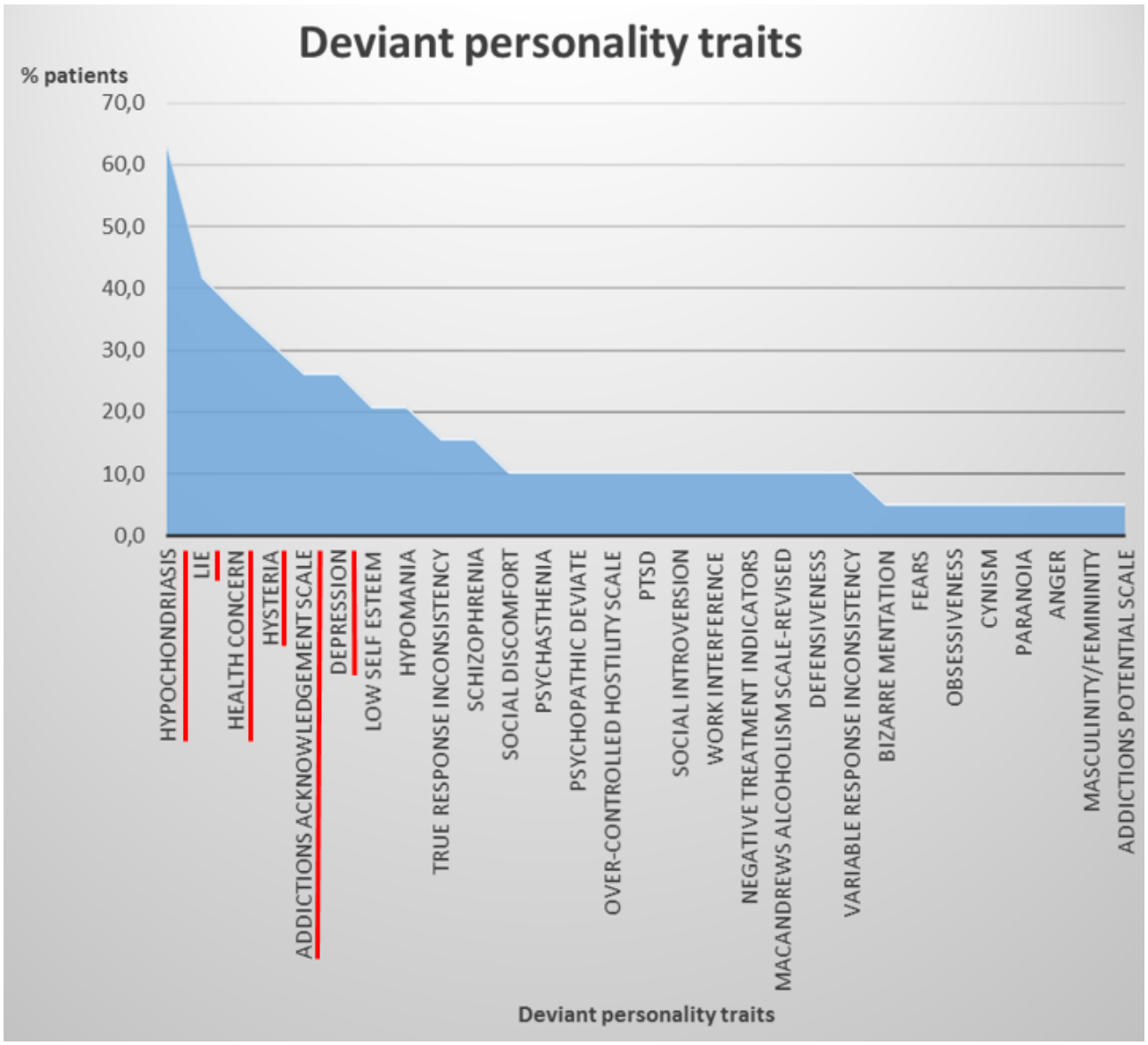
Every patient had a normal neuropsychological exam. The statistical analyses revealed some significant improvements after treatment at the following tests (see Table 4): naming (p=0.038), digit span (p=0.013), Rey list immediate and late recall (respectively p=0.024 and p=244 0.008) and Stroop test with improvements in time (p=0.004) and number of errors (p=0.046). Moreover, there was a significant correlation between the improvement at the digit span scores and improvements in pain sensations (McGill, NWC, R=0.591, p=0.033).

Table 4: Neuropsychological evaluations. Table displays pre and post values expressed in mean ± standard deviations or in medians and (in parenthesis) first and third quartiles, according to data normality. ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; MMSE: Mini Mental State Examination. P values of Wilcoxon analyses are displayed.

* represents significant differences between pre and post data.

Tests		Pre	Post	P value
ADL		6.00 (6.0 to 6.0)	6.00 (6.0 to 6.0)	0.317
MMSE		29.00 (28.5 to 30.0)	30.0 (28.5 to 30.0)	0.864
Digit span test		6.0 (5.0 to 6.0)	6.0 (5.5 to 7.0)	0.013 *
Rey Complex Figure Test	Immediate	42.75 ± 4.79	54.75 ± 9.71	0.024 *
	Deferred	10.0 ± 0.82	10.25 ± 1.71	0.508
	Recognition	14.5 (14.0 to 15.0)	15.0 (13.5 to 15.0)	0.860
	Late Recall	11.0 (7.0 to 14.5)	14.5 (10.5 to 18.0)	0.008 *
Raven's Progressive Matrices		29.75 ± 3.10	30.50 ± 5.20	0.399
Attentional Matrices		53.50 ± 5.32	54.25 ± 3.40	0.301
Wisconsin Card Sorting test	Total	70.25 ± 61.16	63.0 ± 47.90	0.346
	Preservative errors	18.75 ± 17.15	14.25 ± 9.54	0.259
	Non preservative errors	19.50 ± 17.02	19.0 ± 18.53	0.702
	Failures	2.25 ± 2.63	2.75 ± 1.50	0.309

The descriptive analysis of the psychological profile of patients (MMPI-2) showed that 63.2% of patients presented with scores above normal for hypochondriasis. Scores above normal were also observed for lie (42.1%), health concern (36.8%), hysteria (31.6%), addictions acknowledgement scale (26.3%) and depression (26.3%). Detailed results of psychological profile are displayed in Figure 2 and 3.


Deviant personality traits
% patients
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
HYPOCHONDRIASIS
LIE
HEALTH CONCERN
HYSTERIA
ADDICTIONS ACKNOWLEDGEMENT SCALE
DEPRESSION
LOW SELF ESTEEM
HYPOMANIA
TRUE RESPONSE INCONSISTENCY
SCHIZOPHRENIA
SOCIAL DISCOMFORT
PSYCHASTHENIA
PSYCHOPATHIC DEVIATE
OVER-CONTROLLED HOSTILITY SCALE
PTSD
SOCIAL INTROVERSION
WORK INTERFERENCE
NEGATIVE TREATMENT INDICATORS
MACANDREWS ALCOHOLISM SCALE-REVISED
DEFENSIVENESS
VARIABLE RESPONSE INCONSISTENCY
BIZARRE MENTATION
FEARS
OBSESSIVENESS
CYNISM
PARANOIA
ANGER
MASCULINITY/FEMININITY
ADDICTIONS POTENTIAL SCALE
Deviant personality traits

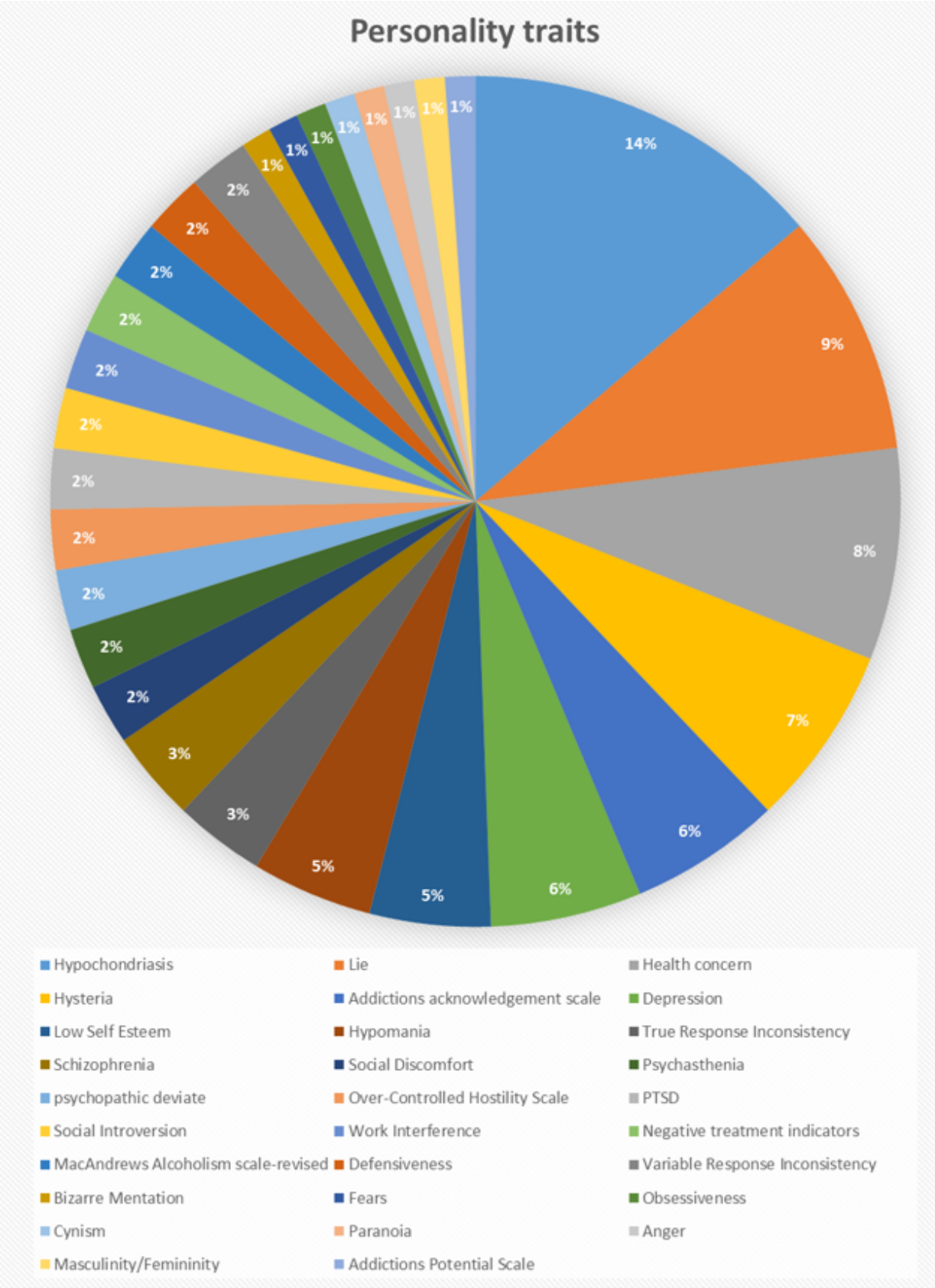


Figure 2 and 3: Personality traits. Figure shows the representation of deviant personality traits amongst participants.

11.3 PARTICIPATION, FUNCTION AND PROPRIOCEPTION

Results are exposed in Table 5. The statistical analyses of RMDQ and kinematics data revealed a significant improvement in participation (RMDQ, $p<0.001$), trunk functionality (Maximal range of motion – Rotation, $p=0.002$; Average range of motion – Rotation, $p=0.008$), and proprioception (Repetition Index – Rotation, $p=0.024$). The scale RMDQ reached a clinical relevance of change, improving more than its minimal clinically important difference (MCID). Indeed, the mean improvement was 4.4 ± 4.04 points whilst its MCID for low back pain patients is 3.5 points [54].

Table 5: Physical Therapy evaluations. Table shows pre and 272 post average values (± standard deviations) for participation (RMDQ), function (Maximal and Average Rotation) and proprioception (Repetition Index). RMDQ: Roland and Morris Disability Questionnaire.

* represents significant differences between pre and post data (t-test).

Maximal and Average Rotation are the range of motion during ten trunk's rotation, expressed in degree, whilst Repetition Index is an index of proprioception from 0 to 1, where 1 corresponds to the maximal accuracy in performing the same excursion of range of motion during the ten repetition.

Tests		**Pre**	**Post**	**P value**
RMDQ		14.07 ± 4.59	8.28 ± 6.49	< 0.001 *
Kinematic Data	Maximal Rotation	52.92 ± 22.26	69.39 ± 17.43	0.002 *
	Average Rotation	33.55 ± 20.32	53.20 ± 20.94	0.008 *
	Repetition Index	0.59 ± 0.15	0.74 ± 0.17	0.024 *

The improvements in participation (RMDQ) correlated with the improvements reported by the patients on the GIC scale (Pearson R= 0.592, $p=0.006$), NRS (Pearson R= 0.598, $p=0.006$), MPQ PRI-TOT (Pearson R= 0.711, $p<0.001$) and MPQ NWC (Pearson R= 0.629, $p=0.003$).

12. DISCUSSION

Chronic pain has become a major health concern worldwide. Pharmaceutical companies are currently addressing the crisis of prescription drug abuse or misuse through the development of abuse deterrent

formulations of opioid analgesics, addiction treatments, medication to treat opioids overdoses, and non-opioid drugs [Cohen et al. 2018][110]. So far, the current treatments are most of all centered on patients' symptoms, proposing to treat pain with pharmacotherapy including simple analgesics, tricyclic antidepressants, tramadol, gabapentin, duloxetine or pregabalin, cyclobenzaprine, pregabalin, duloxetine, milnacipran, topical analgesics (capsaicin, lidocaine, salicylates), and opioids depending on the clinical conditions [Kroenke et al. 2009][111]. However, it is desirable to develop 292 a way to offer more non pharmacological opportunities for chronic pain. Here we propose a different approach. Knowing that the pre-existing psychological profile of patients and the somatic misperception can influence painful symptoms, we focused our non-pharmacological treatment on the restoration of a correct body image, using multisensorial feedback to guide the physiotherapeutic rehabilitation. Thus, our treatment could be considered a "sensory cortical rehabilitation" acting on symptom psychological processing. In line with this assumption, GIC was positive in most of the cases.

The detailed psychological and physical therapy examinations before and after treatment showed a significant improvement in pain perception, QoL, mood, participation, function as improvements in maximal and average range of motion rotation and proprioception, without any side effects. The pain rating scales showed significant decrease in the amount of pain, both quantitatively and qualitatively. Indeed, participants reported decreased pain intensity at the NRS scale and at the BPI scale. This latter scale also showed reduction of interference between pain and their daily life activities.

The McGill pain questionnaire also showed a significant reduction of words used to qualify the pain sensations.

The chronic pain state can trigger a cascade of changes in psychological processes [Simons et al. 2014][112] that seem to qualify, according to our results, for a treatment with VR. Indeed, previous studies demonstrated that chronic pain can affect various cognitive functions, such as attention, verbal memory and executive functions [Moriarty et al. 2011][113]. In line with these reports, our results showed significant improvements in such functions after treatment, with significant correlations between cognitive improvements and reduction of pain sensation. Thus, our results demonstrated that this VR-based treatment was able to act on the multidimensional aspects of pain, improving pain sensations, quality of life, cognitive functions, together with functional and proprioceptive aspects. Regarding the 314 latter point, previous studies showed that VR could improve movement and body position perception [Harvie et al. 2017][114]. In chronic neuropathic pain, a VR-based treatment could induce analgesia in association with an improved embodiment sensation [Pozeg et al. 2017][115].

In line with early reports, our patients presented with abnormal levels of hypochondria, depression, hysteria and health concerns, as shown by the MMPI analyses [Mongini et al. 2000][116]; [Slesinger et al. 2002][117]; [Applegate et al. 2005][118]; [Kato et al. 2017][119]. The MMPI has been used to classify psychological traits of patients with chronic pain. These personality traits of hypochondria, depression and hysteria have been shown to play a role in the chronicization of pain [Mongini et al. 2005][120] and may increase the affective dimension of pain [Mongini et al. 2009][121]. Thus, it appears indicated to include the MMPI in the clinical evaluation of chronic pain patients in order to provide the best-personalized care for each of them.

Our results open a new study perspective and further studies are necessary to define the best treatment duration. In which manner might these improvements effect patients' motor and functional activities? How such a VR treatment can reduce analgesic drug intake? What are the benefits of this kind of treatment with respect to the traditional ones? Certainly, here we link altered behavioural processes to chronicization of the symptom and we begin to provide an answer to the need for care than the traditional. We acknowledge the absence of a control group in this study. These data serve as preliminary evidence and the results should be verified with a randomized clinical trial.

Surely, not all patients report being satisfied with available treatments for chronic pain and there is a pressing need to find new, more efficient therapies for this syndrome which has a very high prevalence [Harstall & Ospina 2003][122] and elevated healthcare costs [Leader et al. 2014][123]; [Park et al. 2012][124]; [Andrew et al. 2014][125]. A plentiful research agenda should include the identification of cures without side effects, which does not induce any dependence, and generates strong motivation in the participants for the practicability and novelty 336 of the therapeutic approach [Kizony et al. 2003][126]; [Jack et al 2001][127]; [Mongini et al. 2009][121].

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